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Abstract: BACKGROUND The present study sought to evaluate the incidence of cerebrovascular events in a large cohort of patients with Brugada syndrome (BrS) analysing possible predictors, clinical characteristics and prognosis of cardioembolic events secondary to atrial fibrillation. METHODS A total of 671 consecutive patients (age 42.1 ± 17.0 years; men 63%) with a diagnosis of BrS were retrospectively analysed over a mean follow-up period of 10.8 ± 5.5 years. The diagnosis of ischemic stroke was made according to the AHA/ASA guidelines using computed tomography (CT) and angio-CT in the emergency department. RESULTS Among 671 patients with BrS, 79 (11.8%) had atrial fibrillation. The incidence of cardioembolic stroke in patients with BrS and atrial fibrillation was 13.9% (11 events). These patients had a low CHA2DS2Vasc score (82%, 0 and 1). Patients with transient ischemic attack/stroke were more frequently asymptomatic (91 vs. 25%; $P < 0.0001$) and older (59.4 ± 11.2 vs. 43.9 ± 16.7; $P = 0.004$) as compared with those without cerebrovascular events. CONCLUSION The incidence of cardioembolic stroke in patients with BrS and atrial fibrillation was unexpectedly high. The cerebrovascular accidents were often the presenting clinical manifestation and were significantly associated with asymptomatic atrial fibrillation and older age. CHADS2 and CHA2DS2Vasc scores did not predict the unexpectedly high risk of thromboembolic events in this group of patients. The use of more invasive diagnostic tools might be useful in order to increase the rate of atrial fibrillation detection.

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Background **The present study sought to evaluate the incidence of cerebrovascular events in a large cohort of patients with Brugada syndrome (BrS) analysing possible predictors, clinical characteristics and prognosis of cardioembolic events secondary to atrial fibrillation.**

Methods **A total of 671 consecutive patients (age 42.1 ± 17.0 years; men 63%) with a diagnosis of BrS were retrospectively analysed over a mean follow-up period of 10.8 ± 5.5 years. The diagnosis of ischemic stroke was made according to the AHA/ASA guidelines using computed tomography (CT) and angio-CT in the emergency department.**

Results **Among 671 patients with BrS, 79 (11.8%) had atrial fibrillation. The incidence of cardioembolic stroke in patients with BrS and atrial fibrillation was 13.9% (11 events). These patients had a low CHA_2DS_2Vasc score (82%, 0 and 1). Patients with transient ischemic attack/ stroke were more frequently asymptomatic (91 vs. 25%; $P<0.0001$) and older (59.4 ± 11.2 vs. 43.9 ± 16.7; $P=0.004$) as compared with those without cerebrovascular events.**

Conclusion **The incidence of cardioembolic stroke in patients with BrS and atrial fibrillation was unexpectedly high. The cerebrovascular accidents were often the presenting clinical manifestation and were significantly associated with asymptomatic atrial fibrillation and older age. $CHADS_2$ and CHA_2DS_2Vasc scores did not predict the unexpectedly high risk of thromboembolic events in this group of patients. The use of more invasive diagnostic tools might be useful in order to increase the rate of atrial fibrillation detection.**

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Keywords: atrial fibrillation, Brugada syndrome, cerebrovascular events, cryptogenic stroke

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Introduction

Brugada syndrome (BrS) is an inheritable syndrome characterized by coved-type ST-segment elevation in the right precordial leads (V_1 through V_3) and increased risk of ventricular fibrillation/sudden cardiac death (SCD) in the absence of structural heart disease.[1] The prevalence of atrial fibrillation in patients with BrS is highly variable ranging from 25 to 39% in older studies[1–3] and from 9 to 19%[4–6] in the most recent studies. Of note, the initial report on the Brugada syndrome reported that two out of eight affected individuals had paroxysmal atrial fibrillation[1]; one of them experienced episodes of atrial fibrillation soon after birth.

The incidence of cerebrovascular events such as transient ischemic attack (TIA) and stroke related to thromboembolism in patients with BrS and atrial fibrillation has not been investigated yet. As a matter of fact, the predictive value of the CHA_2DS_2Vasc score for assessing the risk of cerebrovascular thromboembolic events in this population is still unknown.

The present study sought to evaluate the incidence of cerebrovascular events in a large cohort of patients with BrS analysing possible predictors, clinical characteristics and prognosis of atrial fibrillation-related cerebral thromboembolism.

Methods

Patient population

Since 1992, all consecutive patient diagnosis with BrS have been included in a registry and followed in a prospective fashion. The ethics committee of the Universiteit Ziekenhuis Brussel – Vrije Universiteit Brussel approved all aspects of the registry. A total of 671 consecutive patients with a diagnosis of BrS from the Heart Rhythm Management Centre, Universitair Ziekenhuis Brussel were included. All patients showed a typical electrocardiographic Brugada pattern with or without a sodium channel blocker challenge, as previously reported.[7] Underlying structural cardiac abnormalities were excluded in all patients with noninvasive methods (echocardiogram, stress test and nuclear magnetic resonance) or invasive methods (coronary angiography, left and right ventriculography) used at the discretion of the treating physician. Informed consent was obtained from all patients, and clinical data, including data on age, sex,

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family history of SCD, history of syncope episodes, history of ventricular fibrillation episodes, and ventricular fibrillation induction during an electrophysiological study were obtained from patient records. Importantly, many drugs have been reported to induce the type 1 BrS pattern and/or (fatal) arrhythmias in BrS patients. Therefore, patients with BrS were recommended not to use these drugs or to use them only under controlled conditions.[8]

Ajmaline challenge

Ajmaline (1 mg/kg) was administered intravenously over a 5-min period to unmask the diagnostic ECG pattern of BrS in case of a nondiagnostic baseline electrocardiogram and suspicions of Brugada syndrome. The test was considered positive for BrS only if a coved-type ECG pattern was documented in one right precordial lead (V_1–V_3). An Ajmaline challenge was performed in all patients with a history of aborted sudden death or family history of aborted sudden death, in patients with history of syncope or presyncope, in patients with supraventricular arrhythmias, in all new diagnoses of atrial fibrillation, in patients with cryptogenetic stroke usually before the implantation of a cardiac loop ECG recording, in those with type 2 or 3 BrS, and in family members of BrS patients.

Implantable cardioverter defibrillators

The decision to perform epicardial or endocardial lead implantation or to place the device in a thoracic or subcostal pocket was made according to patient's age, anthropometric characteristics, and level of physical activity, as previously described.[9] The choice between single-chamber and dual-chamber devices was driven by the presence of previous episodes of supraventricular arrhythmias or evidence of sinus node dysfunction and patient's activity in order to prevent inappropriate shocks, as previously described.[10] Implantable cardioverter defibrillator (ICD) programming at the time of implantation changed over time. After our initial experience, the ventricular fibrillation detection rate was increased from 180 to more than 200 beats/min for primary prevention implantations, and a monitor zone was added.[11] Conversely, in patients undergoing ICD therapy for secondary prevention,[12] a monitor zone (>150 beats/min) and a fast VT zone (180–200 beats/min) with antitachycardia pacing and shocks were programmed in all cases, and supraventricular tachycardia discriminators were activated if available.

Supraventricular arrhythmias, incidence and treatments

All patients were evaluated for the incidence of atrial fibrillation and atrial flutter. We evaluated the pharmacological therapy and eventually the catheter ablation treatment.[13] In patients with atrial fibrillation, we administrated anticoagulation following the $CHADS_2$ score guidelines from 2004[14] and from 2012 the CHA_2DS_2VASc score.[15] All patients having undergone catheter ablation for atrial fibrillation received anticoagulation therapy for a minimum of 3 months immediately after the procedure independently of thromboembolic risk.

Electrophysiological study

Electrophysiological study (EPS) included basal measurements of conduction intervals and programmed ventricular stimulation, as previously reported by our group. A patient was considered inducible if a sustained ventricular arrhythmia (ventricular fibrillation, polymorphic VT, or monomorphic VT lasting greater than 30 s or requiring emergency intervention) was induced.[16] Genetic testing was recommended to all patients with diagnosis of BrS.

Cerebrovascular events

In detail, the diagnosis of ischemic stroke was done according to the AHA/ASA Guidelines[17] (Class I, Level of Evidence A) using CT and angio-CT in the emergency department. Magnetic resonance imaging was also performed in all patients after the acute phase in order to assess the specific characteristics of the ischemic lesions. An echocolor Doppler of the carotid artery was performed in all patients after a stroke event. Patients with stroke related to atrial fibrillation presented cardioembolic events. Neuroimaging findings supporting cardioembolic stroke included simultaneous or sequential strokes in different arterial territories. All patients also underwent a transcranial Doppler to exclude a patent foramen ovale.

Demographic and clinical data, risk factors, presenting symptoms, findings from brain imaging and prognosis were retrospectively collected for each patient presenting any cerebrovascular thromboembolic event.

Follow-up

Clinical follow-up of patients consisted of physical examination and ECG performed at least every 6 months in case of symptomatic and device therapy patients and every 2 years otherwise. Clinical data were regularly collected. Follow-up of ICDs was performed at 1 and 3 months after implantation and thereafter every 6 months in the outpatient clinic, combined with remote device monitoring provided by the cardiac device company. All available electrograms of appropriate and inappropriate shocks were analysed by at least two independent investigators. Malignant ventricular arrhythmias were defined as: sudden death or appropriate implantable cardioverter defibrillator therapy. Atrial fibrillation was specifically searched with 24-h Holter monitoring and implantable loop recorder devices. The former ones were performed every year in asymptomatic patients and every 3–6 months in symptomatic ones. The loop recorders were implanted in those patients with palpitations and negative Holter examinations.

Statistical analysis

Continuous variables are expressed as mean ± SD or median and range as appropriate. Categorical variables are expressed as absolute and relative frequencies. Comparisons of continuous variables were done with a Student's *t*-test or the Mann–Whitney *U*-test as appropriate. The chi-square test or the Fisher's exact test was used to compare categorical variables as appropriate. A *P* value less than 0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS software (SPSS v20, Chicago, Illinois, USA).

Results

Study population

In our registry, 671 patients (age 42.1 ± 17.0 years; men 63%) with BrS were collected; a spontaneous type 1 ST elevation was observed in 17% of patients ($n = 113$). The main characteristics of the study population are detailed in Table 1. The mean follow-up after the BrS diagnosis was 10.8 ± 5.5 years.

Seventeen patients (3%) had aborted sudden death as first manifestation and 194 (29%) had at least one episode of syncope. A family history of sudden death was present in 43% of patients ($n = 290$); history of atrial fibrillation was also present in a considerable number of patients (12%; $n = 79$). Genetic test was performed in 312 patients (46%) and a genetical mutation was found in 24% of all the tests ($n = 74$). The mean $CHADS_2$ score and CHA_2DS_2Vasc score were, respectively, 0.14 ± 0.42 and 0.57 ± 0.77. Specifically, 596 patients (88.8%) with BrS had a $CHADS_2$ score of 0, 58 patients (8.6%) presented a score of 1, 16 patients (2.4%) presented a score of 2, and only 1 patient (0.2%) exhibited a $CHADS_2$ score of 3. In terms of CHA_2DS_2Vasc score, 375 patients (55.9%) presented 0, 235 patients (35.0%) had 1, 41 patients (6.1%) exhibited 2, 16 patients (2.4%) presented 3, and finally 3 and only 1 patient (0.4% and 0.1%), respectively, presented CHA_2DS_2Vasc scores of 4 and 5.

Atrial fibrillation

Among 671 patients with BrS included in our registry, 79 (11.8%) presented atrial fibrillation and atrial flutter. Of them, 69 (87.3%) were paroxysmal, 7 persistent (8.9%) and 3 permanent (3.8%). In 32 patients (40.5%), atrial fibrillation preceded the diagnosis of BrS; the first detection of atrial fibrillation was obtained through a standard 12-lead ECG in 31 patients (39.2%), with a 24-h Holter monitoring in 34 (43.1%), and in the Holter memory of ICDs in 14 (17.7%). In seven of these patients (21.9%), the subsequent diagnosis of BrS was unmasked by sodium channel blockers, which were administered to prevent atrial fibrillation episodes; none of these patients actually presented TIA/stroke.

Out of 79 patients with atrial fibrillation, in 32 (40.5%), atrial fibrillation was already known before the BrS diagnosis and in 47 (59.5%), atrial fibrillation was completely asymptomatic and the diagnosis was made accidentally or during clinical investigations after the diagnosis of BrS or stroke. The characteristics of these two groups have been compared in Table 2.

Thirty patients (38.0%) had a previous ICD implantation and inappropriate shocks because of rapid atrial fibrillation were documented in nine of them (30%). The mean age at the time of diagnosis was 46.1 ± 15.7 years. All patients with atrial fibrillation were treated with sotalol as first-line medication. A total of 23 patients (29.1%) with atrial fibrillation refractory of sotalol underwent a catheter ablation procedure using radiofrequency or Cryoballoon technology (6 and 17, respectively). After a mean follow-up time of 35.0 ± 25.4 months (median 36 months), 17 patients (73.9%) did not present any AT/atrial fibrillation relapses after the index procedure.

Among patients with atrial fibrillation, the mean $CHADS_2$ score and CHA_2DS_2Vasc score were, respectively, 0.21 ± 0.50 and 0.65 ± 0.88. Specifically, 65 patients (82.2%) with BrS had a $CHADS_2$ score of 0, 11 patients (13.9%) presented a score of 1, and 3 patients (3.8%) presented a score of 2. In terms of CHA_2DS_2Vasc score, 43 patients (54.4%) presented 0, 26 patients (32.9%) had 1, 6 patients (7.6%) exhibited 2, 3 patients

Table 1 Study population

Age (years)	42.1 ± 17.0
Sex: male	422 (63)
Spontaneous type 1 ST elevation	113 (17)
Family history of sudden death	290 (43)
ICD implantation	183 (27)
Atrial fibrillation	79 (12)
Genetic testing	312 (46)
Genetic mutations[a]	74 (24)
CHADS score	0.14 ± 0.42
CHA_2DS_2Vasc score	0.57 ± 0.77
Sick sinus syndrome	16 (2)

Categorical variables are expressed as absolute and percentage (in brackets). Continuous variables are expressed as mean ± SD. ICD, implantable cardioverter defibrillator. [a] Percentages are calculated only among patients with genetic test.

Table 2 Comparison of patients with atrial fibrillation known before Brugada syndrome diagnosis with those having atrial fibrillation detection after Brugada syndrome diagnosis

	Atrial fibrillation before BrS diagnosis ($n = 32$)	Atrial fibrillation after BrS diagnosis ($n = 47$)	*P* value
Male sex	22 (69)	30 (64)	0.8
Age (years)	44.4 ± 17.4	43.6 ± 16.1	0.8
Hypertension	6 (19)	7 (15)	0.8
BMI (kg/m^2)	25.5 ± 2.1	24.8 ± 3.2	0.4
CHADS score	0.28 ± 0.58	0.13 ± 0.34	0.2
CHA_2DS_2-VASc score	0.66 ± 0.94	0.60 ± 0.82	0.8
Type 1 ECG pattern	5 (16)	4 (9)	0.5
Genetic mutation[a]	2 (6)	9 (19)	0.2
Malignant arrhythmic events	4 (12)	2 (4)	0.2
Left atrial diameter (mm)	38.1 ± 5.4	38.7 ± 7.3	0.8
TIA/Stroke	1 (3)	10 (21)	0.02

Categorical variables are expressed as absolute and percentage (in parentheses). Continuous variables are expressed as mean ± SD. AF, atrial fibrillation; BrS, Brugada syndrome; TIA, transient ischemic attack. [a] Percentages are calculated only among patients with genetic test.

(3.8%) presented 3, and only 1 patient (1.3%) presented a CHA_2DS_2Vasc score of 4.

Cerebrovascular events

The total number of cerebrovascular events in our study population was 13 (1.9%). Two of them (15%) were excluded from our analysis because no clear relationship with atrial fibrillation and embolic cause could be recognized. Particularly, the first one was a 66-year-old patient with hypertension, dyslipidaemia having experienced a stroke in the irrigation area of the left internal carotid artery symptomatic for aphasia and confusional state; after having documented a 90% stenosis of the left carotid artery, the patient underwent a successful carotid endarterectomy. The second one was a 71-year-old woman having experienced a TIA after a long history of a recurrent breast cancer treated with surgery and radiotherapy. Interestingly, 11 patients with BrS experienced cerebrovascular events, all related to atrial fibrillation (13.9%); specifically, 6 of them (54.5%) presented as cerebrovascular strokes and 5 (45.5%) as transient ischemic attacks. All these patients are described in Table 3. Of note, seven of these patients (63.6%) experienced the cerebrovascular event as the first manifestation of BrS. None of them was under oral anticoagulation at the time that cerebrovascular events occurred.

The clinical characteristics of patients with TIA/stroke related to atrial fibrillation are listed in Table 3. The mean age at presentation was 59.4 ± 11.2 years old (median 62 years old). Three of them (27.2%) presented a spontaneous type 1 ECG pattern. As shown in Table 3, the most common clinical presentation was aphasia and speech disorders (in seven patients, 64%) and left hemiparesis or paralysis (in five patients, 45%). A 49-year-old patient presented a posterior circulation infarction associated with nausea, vertigo, presyncope and de novo diagnosis of atrial fibrillation. Most of the patients presented a complete clinical resolution after the cerebrovascular events (63.6%), two of them exhibited a residual left hemiparesis (18.2%), another one (9.1%) showed a degenerative cognitive impairment after recurrent episodes of embolic strokes and the last one (9.1%) died 1 month and 15 days later from acute mesenterial ischemia. Both patients were under anticoagulation therapy.

Among patients with TIA/stroke and atrial fibrillation, nine patients (81.8%) had a $CHADS_2$ score of 0, another patient (9.1%) presented a score of 1 and the last one (9.1%) exhibited a score of 2. In terms of CHA_2DS_2Vasc score, five patients (45.4%) had 0, four patients (36.3%) had 1, and two patients (9.1%), respectively, presented a score of 2 and 3. The mean $CHADS_2$ score and CHA_2DS_2Vasc score were, respectively, 0.27 ± 0.65 and 0.82 ± 0.98.

As shown in Table 4, patients presenting stroke were significantly older as compared with the age at

Table 3 Patients with Brugada syndrome and atrial fibrillation presenting cerebrovascular events

Patient	Sex	Age at BrS diagnosis	Age at stroke	Age at atrial fibrillation diagnosis	Age at ICD implantation	CHADS before stroke	CHA^2DS^2-VASc before stroke	Conduction disease	Therapy before stroke	Therapy after stroke	Clinical diagnosis	Risk factors	Clinical presentation	Post-TIA/stroke evolution
#1	Male	70	62	70	70	0	0	Yes	Antiplatelet	NOAC	TIA		Aphasia	Complete resolution
#2	Male	67	74	75	74	0	1	No	None	NOAC	TIA		Left hemiparalysis, aphasia	Complete resolution
#3	Male	63	63	63	63	1	1	Yes	No	NOAC	Stroke	Hypertension	Left arm paresis	Complete resolution
#4	Female	79	70	79	79	0	2	Yes	No	NOAC	Stroke		Aphasia, confusion	Cognitive impairment
#5	Male	47	44	47	47	0	0	Yes	No	NOAC	Stroke		Left hemiparesis	Residual paresis
#6	Male	49	49	49	/	0	0	No	No	NOAC	Stroke		Nausea, presyncope, vomiting (posterior stroke)	Complete resolution
#7	Male	63	71	71	/	2	3	No	No	OAC	Stroke	Hypertension Diabetes	Left hemiparesis, aphasia	Exitus 1.5 months later (acute mesenterial ischemia)
#8	Male	37	41	41	/	0	0	No	No	NOAC	TIA		Diplopia	Complete resolution
#9	Male	55	52	50	/	0	0	No	No	NOAC	TIA		Aphasia	Complete resolution
#10	Male	65	65	66	/	0	1	No	No	NOAC	Stroke		Left hemiparesis, aphasia	Complete resolution
#11	Female	61	62	63	61	0	1	No	No	NOAC	TIA		Dysarthria	Complete resolution

AF, atrial fibrillation; BrS, Brugada syndrome; ICD, implantable cardioverter defibrillator; NOAC, novel oral anticoagulants; OAC, oral anticoagulation; TIA, transient ischemic attack.

Table 4 Characteristics of patients with stroke vs. those without stroke in the group of patients with atrial fibrillation

	Patients with stroke ($n=11$)	Patients without stroke ($n=68$)	*P* value
Male sex	9 (82)	43 (63)	0.31
Age (years)	59.4 ± 11.2	43.9 ± 16.7	0.004
Hypertension	2 (18)	12 (18)	0.62
Diabetes mellitus	1 (9)	1 (1)	0.26
BMI (kg/m^2)	25.1 ± 3.1	24.9 ± 2.5	0.81
CHADS score	0.27 ± 0.65	0.13 ± 0.41	0.34
CHA_2DS_2-VASc score	0.82 ± 0.98	0.65 ± 0.88	0.56
Type 1 ECG pattern	2 (18)	7 (10)	0.60
ICD presence	6 (55)	24 (35)	0.32
Genetic mutation[a]	1 (25)	10 (29)	0.69
Malignant arrhythmic events	1 (9)	5 (7)	0.61
Asymptomatic atrial fibrillation	10 (91)	17 (25)	<0.0001
Left atrial diameter (mm)	40.1 ± 2.1	38.1 ± 6.9	0.35

Categorical variables are expressed as absolute and percentage (in parentheses). Continuous variables are expressed as mean ± SD. ICD, implantable cardioverter defibrillator. [a]Percentages are calculated only among patients with genetic test.

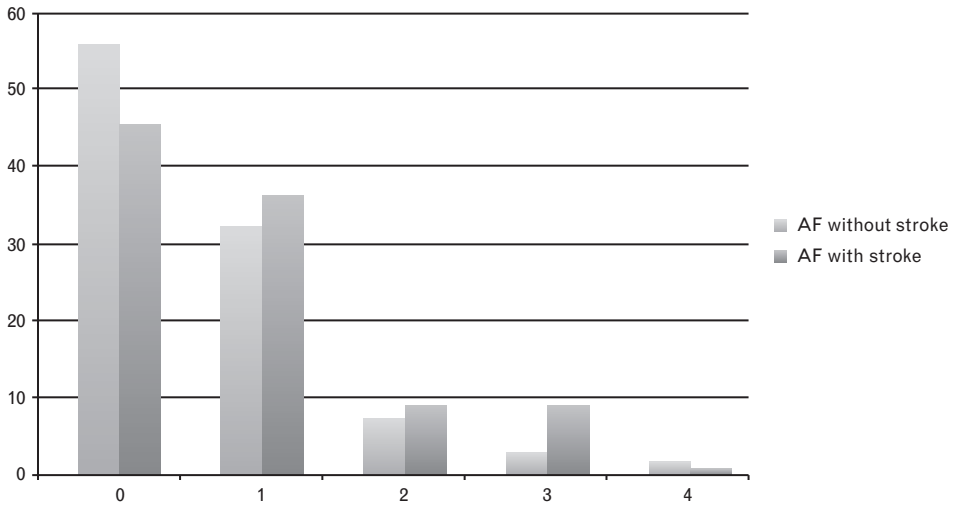
presentation of those presenting atrial fibrillation and BrS without any cerebrovascular events (59.4 ± 11.2 vs. 43.9 ± 16.7 years old; $P=0.004$). Of note, $CHADS_2$ and CHA_2DS_2Vasc scores did not significantly differ between the two study groups. Although the left atrial diameter was slightly higher in the TIA/stroke group, it was not significantly different between the two groups (Table 4). Figure 1 shows the distribution of CHA_2DS_2-Vasc score in patients with atrial fibrillation and TIA/stroke compared with those with atrial fibrillation without TIA/stroke. Of note, most of the patients presenting a cerebrovascular event exhibited a CHA_2DS_2Vasc score of 0 and 1 (respectively, 45 and 36%). No significant relationship was found between malignant arrhythmic events and cerebrovascular accidents during the follow-up. Significantly, 91% of patients presenting atrial fibrillation-related TIA/strokes had asymptomatic episodes of atrial fibrillation, diagnosed by further clinical investigations or recorded by ICD Holter memory, compared with 25% of asymptomatic atrial fibrillation in patients without cerebrovascular accidents ($P<0.0001$). The diagnosis of atrial fibrillation was obtained while checking the ICD in five patients (45.4%), during in-hospital monitoring after the cerebrovascular accidents in two patients (18.2%), and by means of ECG and 24-h Holter monitoring in the remaining four patients (36.4%). The other clinical characteristics were similar in both populations.

Discussion

The present study showed that: the incidence of cardioembolic stroke in patients with BrS and atrial fibrillation was unexpectedly high at 13.9%; these patients had a low CHA_2DS_2Vasc score (82% of them with a score of 0 or 1), which was similar to those patients with BrS and atrial fibrillation without TIA/stroke; in 63.6% of patients, the cerebrovascular accident was the first manifestation of BrS, occurring before the diagnosis; among patients presenting TIA/stroke, a significantly higher number of asymptomatic patients was found when compared with those without cerebrovascular events (91 vs 25%; $P<0.0001$); patients experiencing a cardioembolic TIA/stroke were significantly older than those without a cerebrovascular event.

The incidence of cardioembolic stroke among patients with BrS and atrial fibrillation was unusually high, accounting for about 14%. Of note, the $CHADS_2$ score

Fig. 1



The histogram shows the distribution of CHA_2DS_2Vasc score in patients with atrial fibrillation and transient ischemic attack/stroke (dark grey columns) compared with those with atrial fibrillation without transient ischemic attack/stroke (light grey columns). Interestingly, most of the patients with atrial fibrillation presenting a cerebrovascular event exhibited a CHA_2DS_2Vasc score of 0 and 1 (respectively, 45 and 36%).

and CHA_2DS_2Vasc scores were low both in the study population and in those patients with atrial fibrillation.

Respectively, a $CHADS_2$ of 0 represented 89% of all patients and a CHA_2DS_2Vasc score of 0 and 1 both constituted the 91% of the overall study population. Similarly, patients with atrial fibrillation exhibited mean $CHADS_2$ and CHA_2DS_2Vasc scores of 0.21 ± 0.50 and 0.65 ± 0.88, respectively. Specifically, a $CHADS_2$ of 0 represented 82.2% of these patients, 13.9% presented a score of 1, and 3.8% exhibited a score of 2. A CHA_2DS_2-Vasc score of 0 and 1 both constituted the 87% of all patients with BrS and atrial fibrillation; only 7.6% exhibited a CHA_2DS_2Vasc score of 2, 3.8% presented 3, and only 1.3% presented a CHA_2DS_2Vasc score of 4. As Fig. 1 shows, patients with atrial fibrillation-related cardioembolic event exhibited a similar distribution in $CHADS_2$ and CHA_2DS_2Vasc scores; most of them exhibited a theoretically low profile risk for thromboembolic events at the time TIA/stroke occurred (81.8% of them presented both a $CHADS_2$ of 0 and a CHA_2DS_2Vasc score of 0/1). Only two patients (18.2%) in the group of atrial fibrillation and TIA/stroke had, respectively, a $CHADS_2$ at least 1 and a CHA_2DS_2Vasc score at least 2. These findings highlighted that $CHADS_2$ and CHA_2DS_2Vasc scores did not correlate with a higher risk of thromboembolic events in the specific subset of BrS patients with atrial fibrillation, in contrast with literature data on the general population.[13,14,18] In fact, the annual adjusted stroke rate has been reported to be 1.9% for patients with $CHADS_2$ of 0, 2.8% for those with $CHADS_2$ of 1, 4.0% for those with $CHADS_2$ of 2.[18] Similarly, the annual adjusted stroke rate has been reported to be 0% for patients with CHA_2DS_2Vasc score of 0, 1.3% for those with CHA_2DS_2-Vasc score of 1, 2.2% for those with CHA_2DS_2Vasc score of 2, and 3.2% for those having a CHA_2DS_2Vasc score of 3.[18] Conversely to the literature data reporting high reliability of $CHADS_2$ and CHA_2DS_2Vasc scores for predicting cerebrovascular accidents on the general population presenting atrial fibrillation, these scores do not seem to adequately predict the occurrence of cardioembolic events in patients with BrS and atrial fibrillation.

Of note, in 7 out of 11 patients (63.6%), the cerebrovascular accident was the presenting manifestation, occurring before the diagnosis of BrS. This might suggest that a cardioembolic cryptogenic TIA/stroke should raise the suspicion of atrial fibrillation episodes possibly associated with underlying BrS, especially in younger patients.

Interestingly, most of the patients having experienced TIA/stroke had asymptomatic episodes of atrial fibrillation (91%) in contrast with those without cerebrovascular events who presented only 25% of asymptomatic atrial fibrillation. An unrecognized atrial fibrillation might hypothetically result in higher risk of thromboembolic events because neither antiarrhythmic nor anticoagulation therapies have the chance to be introduced in these patients. As the incidence of atrial fibrillation in patients with BrS has been reported in a considerable number of BrS patients[1–5] and the overall prevalence of asymptomatic episodes in our study population is considerably high (34%), especially in those presenting TIA/stroke (91%), the use of more invasive diagnostic tools, such as loop recorder implantation might be hypothetically considered in this specific group of patients in order to increase the rate of atrial fibrillation detection. As a matter of fact, previous studies have shown that prolonged and continuous rhythm monitoring are able to critically improve the detection of silent episodes of atrial fibrillation.[19–21] Implantable subcutaneous cardiac monitors and external loop recorders have been demonstrated to be effective in the early detecting of atrial tachyarrhythmias by avoiding delays in the therapy evaluation.[22–24] Specifically, a recent prospective and randomized study showed that a 3-year monitoring by insertable cardiac monitors in cryptogenic stroke patients resulted in a significantly higher atrial fibrillation detection rate compared with routine care.[24] Given the frequency of asymptomatic first episodes and the long median time to detection, the authors concluded highlighting the limitations of the traditional atrial fibrillation detection methods.

Moreover, as the $CHADS_2$ and CHA_2DS_2Vasc scores do not predict cerebrovascular events in patients with BrS and atrial fibrillation, the anticoagulation strategy should not be based anymore on such scores and should be theoretically revised for this specific subset of patients. However, our findings have to be confirmed by further larger, prospective studies. Of note, in our study, the pharmacologic therapy of those patients with atrial fibrillation and BrS was based on sotalol. However, in literature, also hydroquinidine has been proven to be effective and safe in preventing recurrences of atrial fibrillation and atrial flutter in patients with Brugada pattern.[6]

Interestingly, those patients experiencing a cardioembolic TIA/stroke were significantly older than those without a cerebrovascular event (59.4 ± 11.2 vs. 43.9 ± 16.7, $P = 0.004$); thus, the age seems to be associated with a higher risk for developing cerebrovascular embolic accidents. No other characteristics were found to be significantly associated with higher thromboembolic risk. However, larger and prospective studies would be needed to confirm our findings and possibly find further predictors of cardioembolic TIA/stroke in this specific population.

Limitations

Some limitations can be found in our study. The present work is a retrospective and single-centre study. Moreover, as the number of cerebrovascular events was relatively small ($n = 11$), multivariate analysis and Kaplan–Meier curves were not performed. As patients with a negative CT and a clinical diagnosis of TIA were planned for elective magnetic resonance imaging and these

further examinations were then performed in other centers, we were not able to achieve the information about MRI.

A prospective study, directly involving also the Neurological Department, to assess, on one hand, the incidence of Brugada pattern among patients with stroke and, on the other hand, the incidence of stroke among patients with a previous diagnosis of Brugada pattern would be desirable.

Conclusion

The current study documented an unusually high incidence of cerebral embolism events in patients with BrS and atrial fibrillation as compared with the expected incidence using current scores. The reason for this abnormal high incidence of thromboembolism events is unclear. Because of the many asymptomatic episodes of atrial fibrillation in this population, active monitoring (ICD remote monitoring, implantable loop recording) may be justified.

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